Biliary complications following liver transplantation

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Introduction

Biliary complications are a major cause of morbidity and graft failure after liver transplantation. Although advances in the surgical technique of liver transplantation have led to a better overall outcome and fewer surgical complications, biliary complications still occur in 10–40% of recipients and are associated with mortality rates of 8–15%. The high biliary complication rate in liver transplantation can partly be explained by the increasing diversity of liver grafts used for transplantation in recent years. The shortage of grafts available has led to the increased use of livers that have been donated after cessation of blood flow in the donor, or so-called donation after circulatory death (DCD) donors. The organs of DCD donors suffered an extra period of warm ischemia compared to donation after brain death (DBD) livers, and are therefore more susceptible to develop biliary complications. The use of DCD organs and other extended-criteria donor livers is inevitable in an attempt to scale down the worldwide shortage of organs. In order to expand the pool of potential donors, split-liver transplantation and living donors have also evolved as surgical alternatives and numbers have increased in recent years, providing particularly young children with an opportunity to receive a graft in time. The rate of split- and living donor transplantation shows large variations among countries. In some Asian countries, the percentage of living-donor liver transplantation rate reaches almost 100%, whereas in the US and most European countries the percentage is around 10%. Diversity in the quality and type of transplanted organs, variations in recipient risk factors, and variations in the applied surgical technique lead to a diversity in biliary complications that may occur after liver transplantation. The three most common types of biliary complications can are: non-anastomotic strictures (NAS), anastomotic strictures and biliary leakage. These and other less frequent biliary complications are summarized in box 32.1 and will be discussed in this chapter. First, aspects of organ procurement that are relevant for the prevention of biliary complications will be covered. Hereafter surgical aspects of bile duct reconstruction will be discussed, followed by a discussion of diagnostic and imaging methods and a description of the pathogenesis, clinical presentation, and management of the various types of biliary complications after liver transplantation.
Table 1.
Classification of biliary complications after liver transplantation\(^4\)

1. Biliary leakage
   1A. From biliary anastomosis
   1B. From hepatic biopsy or parenchymal injury
   1C. From gallbladder fossa or cystic duct stump
   1D. After removal of biliary drain
2. Anastomotic stenosis of:
   2A. Choledocho-choledochostomy
   2B. Hepatico-jejunostomy
3. Post-transplant cholangiopathy
   3A. Non-anastomotic biliary strictures (of extrahepatic and large intrahepatic ducts)
   3B. Intraductal biliary casts
   3C. Bile duct necrosis with intrahepatic leakage and biloma formation
4. Biliary abnormalities due to hepatic artery stenosis of thrombosis
5. Biliary strictures due to recurrent disease (i.e. primary sclerosing cholangitis)

2. Surgical technique in relation to biliary complications

2.1 Organ procurement and preservation

Efforts to minimize the risk of biliary complications after liver transplantation should start with proper surgical and preservation techniques during the donor procedure. Aspects of liver procurement and preservation that have been demonstrated to reduce the risk of biliary complications include: 1) efforts to minimize ischemic injury of the bile ducts, 2) preservation of the vasculature of the extrahepatic bile duct by avoiding dissection too close to the bile duct, 3) thorough rinsing of the bile duct lumen to remove toxic bile, 4) adequate arterial perfusion of the liver with preservation fluid to preserve the peribiliary capillary plexus and 5) rapid procurement after initiation of cold flushing in the donor.
These aspects are relevant as biliary epithelial cells (cholangiocytes) are very sensitive to ischemia/reperfusion injury. In addition to primary preservation-related ischemic injury, ischemic damage of the peribiliary plexus will result in secondary ischemic injury of the biliary epithelium. The strong relationship between ischemia and bile duct injury is illustrated by studies demonstrating an association between both cold and warm ischemia time and the development of NAS. As long as the cold ischemia time is kept below 10 h, the incidence of NAS is not increased, however more prolonged cold ischemia is clearly associated with a higher risk of these strictures. Warm ischemia time has also been identified as a risk factor in several studies. The relevance of warm ischemia is also illustrated by the high incidence of NAS after transplantation of livers from DCD donors, which suffer an inevitable period of warm ischemia prior to organ procurement.\textsuperscript{5,6}

During organ procurement, surgeons should avoid “stripping” of the extrahepatic bile duct, which will damage its microvascularization. The extrahepatic bile duct should always remain surrounded by an adequate amount of tissue to ensure sufficient blood supply.

Preservation injury results in increased arterial resistance and may cause circulatory disturbances in small capillaries, such as the biliary plexus. Since the blood supply to the biliary tract is solely dependent on arterial inflow, disturbances in the blood flow through the peribiliary plexus may result in insufficient oxygenation and subsequent damage of the biliary epithelium.

Gentle retrograde flushing of the bile ducts with preservation fluid is considered an important method to remove bile from the bile duct lumen. Bile contains bile salts, which are cytotoxic due to their detergent properties. Several studies have shown that bile salts may contribute to toxic damage of the biliary epithelium both during liver preservation and after liver transplantation.\textsuperscript{7,8} At this moment, there is no consensus on which flushing solution is most adequate for successful bile duct preservation.

University of Wisconsin (UW) solution and Histidine-tryptophan-ketoglutarate (HTK) have been recognized as the gold standard preservation solutions. Although some studies have suggested that highly viscous preservation solutions such as the UW solution may result in an incomplete flush-out of the small donor peribiliary arterial plexus, resulting in a higher incidence of NAS,\textsuperscript{9,10} this could not always be confirmed in other studies.\textsuperscript{11} Therefore, it remains debatable whether low viscosity preservation
fluids, such as HTK, are associated with a lower incidence of biliary complications. Adequately powered randomized, controlled trials with long-term follow up are needed to determine whether the type of preservation fluid has an impact on biliary complications after liver transplantation.

One method to overcome inadequate flush-out and preservation of the peribiliary plexus is the application of high pressure arterial infusion of preservation fluid either in vivo during procurement or immediately afterwards during the back-table procedure. Some retrospective studies have shown that additional flushing of the peribiliary plexus by controlled arterial back-table pressure perfusion may result in a considerable reduction in the incidence of NAS. However, a prospective, randomized controlled trial on the efficacy of additional arterial ex situ back-table perfusion demonstrated that this does not prevent NAS after transplantation. Better flush-out and preservation of the peribiliary capillary plexus may also be achieved by machine preservation. Several small studies have shown that end-ischemic hypothermic oxygenated machine perfusion is safely applicable in liver transplantation, and the results look promising. As of this moment, no randomized controlled trials have been finished yet on the outcomes after the use of hypothermic machine perfusion in liver transplantation. Recently, the period between the start of cold flush of the donor organs and the end of liver retrieval has been shown to influence graft survival. During organ procurement, the temperature of the abdominal organs does not drop below 15-20°C, which does not protect the liver and bile ducts against warm ischemic injury. Therefore, after initiation of in situ cold flushing, a donor liver should be excised as rapidly as possible and placed in a bowl with preservation fluid with sterile ice, where it will finally reach a temperature <4°C. Hereafter, the liver should be stored as soon as possible in sterile bags and a box with ice.

**2.2 Biliary reconstruction**

The two main types of biliary reconstruction used in liver transplantation today are: 1) choledocho-choledochostomy, also called the duct-to-duct anastomosis (using either an end-to-end anastomosis or a side-to-side anastomosis), and 2) a hepatico-jejunostomy using a Roux-Y jejunal loop. The use of one type of reconstruction instead of the other
largely depends on the anatomical situation of the recipient’s extrahepatic bile ducts and sometimes the surgical preference.

In case of a duct-to-duct choledocho-choledochostomy, an anastomosis is created between donor and recipient choledochal ducts (common bile duct). An end-to-end anastomosis is generally easier to perform than a side-to-side anastomosis, the former is therefore used more frequently. In a prospective, randomized trial comparing end-to-end anastomosis with side-to-side anastomosis, no major differences in outcome between the two techniques were found. An end-to-end reconstruction restores the physiologic anatomical situation and does not carry the risk of bile sludge or cast formation as can occur in the dead ends of a side-to-side anastomosis.

In case of a Roux-Y hepatico-jejunostomy, an end-to-side anastomosis is constructed between the donor hepatic duct and a Roux-Y jejunal loop created in the recipient. Roux-Y hepatico-jejunostomy is mainly used in patients whose native extrahepatic bile duct is not suitable for anastomosis with the bile duct of the donor liver. The main indications for using a Roux-Y loop for biliary reconstruction are primary sclerosing cholangitis with involvement of the extrahepatic bile duct, biliary atresia, significant size discrepancy between the donor and recipient choledochal duct, and in some cases, retransplantation. Although a hepatico-jejunostomy may be a safe alternative when duct-to-duct anastomosis is not feasible, the disadvantage is that it creates an open connection between the intrahepatic bile ducts of the graft and the bowel lumen. This may result in reflux of small bowel content into the bile ducts and subsequently ascending bacterial migration and (recurrent) cholangitis. An additional advantage of using a choledocho-choledochostomy is easier access for diagnostics and therapy compared with a Roux-Y hepatico-jejunostomy. It is, therefore, generally agreed that the preferred method of biliary reconstruction in liver transplantation should be a choledocho-choledochostomy whenever possible.

Few centers have advocated and reported on the use of a direct connection between the donor bile duct and the recipient duodenum (so-called choledocho-duodenostomy) as a safe alternative to a hepatico-jejunostomy.
2.3 Use of a biliary drain

When reconstructing the biliary system in a liver transplant recipient, this can be done either with or without the insertion of a biliary drain. A biliary drain can be either a T-tube or a straight (open tip) catheter. A T-tube is a flexible tube that is inserted in the choledochal duct in the proximity of the end-to-end anastomosis in case of a choledocho-choledochostomy. This tube allows the bile to drain in two directions: towards the duodenum and outward of the body. Alternatively, a straight catheter can be used, with the advantage of a lower risk of bile leakage upon removal of the drain as it results in a smaller hole in the bile duct after extraction.

Choledocho-choledochostomy reconstructions over T-tubes have been the subject of controversy for many years, but it has nevertheless remained common practice in some transplant centers. Yet, with increasing surgical experience, many centers have begun to abandon the routine use of biliary drains in their liver transplant recipients.\textsuperscript{25,26}

The benefits of using a biliary drain include direct visual evaluation of the quality of bile produced by the recently implanted graft and easy access to the biliary tree for radiologic imaging. Especially in liver grafts that have a higher risk of developing biliary complications (e.g., livers from DCD donors) this could be an advantage. Some studies have suggested that placement of a T-tube may reduce the incidence of anastomotic strictures.\textsuperscript{27} In addition a T-tube may result in adequate decompression of the biliary tree and a reduction of the intraductal pressure, which may subsequently contribute to a lower rate of intrahepatic biliary stricture and leakage.

The main drawback of using T-tubes is their association with an increased rate of biliary complications, especially bile leakage at the site of the drain insertion after its removal occurring in 5–15\% of patients.\textsuperscript{21} In addition, the use of a T-tube increases the risk of ascending cholangitis and peritonitis, due to an open connection of the choledochal duct with the exterior. In one systematic review and meta-analysis of studies focusing on the use of biliary drains in liver transplantation it was concluded that biliary drains such as T-tubes should be abandoned.\textsuperscript{25} Although this meta-analysis showed lower rates of anastomotic and NAS in patients with a T-tube, the incidence of interventions was not diminished in comparison to patients without a T-tube. Patients without a T-tube had fewer episodes of cholangitis and fewer episodes of peritonitis. Yet, patients with or without a T-tube had equivalent outcomes with respect to anastomotic bile leaks or
fistulas, the need for biliary interventions, incidence of hepatic artery thrombosis, retransplantation rate, and mortality due to biliary complications. Two other systematic reviews and meta-analyses show that the use of a T-tube might reduce the incidence of biliary strictures, but that there is no hard evidence towards standardized use in liver transplantation.\textsuperscript{26,27}

The use of alternative devices, such as internal stents, have been reported by some centers, but these stents have been associated with increased rates of serious complications, including obstruction, migration, and erosion with hemobilia.\textsuperscript{28}

The use of biliary drains such as a T-tube in liver transplant recipients, therefore, remains controversial. Probably the only remaining argument to use a T-tube is to allow accurate monitoring and easy access to the biliary tree in liver grafts that carry an increased risk of biliary complications, livers from DCD donors for example.

3. Diagnostic modalities

In most cases, the suspicion of a biliary complication will arise after an increase in liver enzymes is noted. There is no specific pattern to reliably distinguish a biliary complication from other causes of graft dysfunction, although an increase in serum bilirubin, alkaline phosphatase and/or gamma-glutamyl transferase has been suggested to be most specific. Alternatively, patients can present with upper abdominal pain or bacterial cholangitis. In many instances of liver enzyme disturbances, a liver biopsy will be performed after gross biliary congestion and bile duct dilatation have been excluded by ultrasonography. The presence of specific pathologic features such as centrilobular cholestasis and portal changes including edema, predominantly neutrophil polymorph infiltration, ductular proliferation and cholangiolitis may be indicative of the presence of a biliary complication.\textsuperscript{28} These findings, however, are not very specific and can be absent. In addition, biopsy findings are not informative with regard to the type and severity of biliary abnormalities.

The diagnostic work-up of an increase in liver enzymes will always depend on clinical context such as primary disease, time after transplantation, local experience, and information on the biliary anatomy. A general algorithm is provided in Figure 1.
Figure 1: Schematic presentation of the clinical decisions and diagnostic steps in the work-up of a liver transplant recipient with a suspected biliary complication.

3.1 Transabdominal ultrasonography

Transabdominal ultrasonography is a useful primary diagnostic tool when a biliary complication is suspected. Allograft vascularization can be assessed (especially patency of the hepatic artery), fluid collections can be identified, liver parenchyma can be studied, and dilatation of bile ducts can be identified. It should be noted that the transplanted liver behaves differently from a normal liver, in that the biliary system does not dilate as easily in the presence of a biliary obstruction as in normal livers.\textsuperscript{29} This leads to a limited sensitivity of approximately 60% of transabdominal ultrasonography to detect biliary strictures.\textsuperscript{29,30} The predictive value of transabdominal ultrasonography to detect NAS is rather low. Therefore, even a normal ultrasonography of the liver graft in a patient with clinical or biochemical evidence of biliary pathology warrants further investigation.
3.2 Magnetic resonance cholangiography and computed tomography

Magnetic resonance cholangiography (MRC) is an established diagnostic tool for the detection of biliary abnormalities. It has the strong advantage of providing excellent anatomic information without being invasive. MRC is useful in the detection of both leakages and strictures. The use of an additional magnetic resonance imaging or magnetic resonance angiography scanning protocol can also provide information about the liver parenchyma and vasculature. The reported sensitivity and specificity of MRC for the detection of biliary complications is well over 90%. After ultrasonography, MRC is the preferred diagnostic tool when a biliary complication is suspected. However, one study showed that MRC is indeed a reliable tool to detect or exclude biliary complications, but that its reliability to grade severity of these strictures is low. Recently, also computed tomography (CT) scanning has been suggested to be of value for the detection of post-transplant biliary complications – it has a higher spatial resolution compared to MRC. However, the experience with CT cholangiography after liver transplantation is very limited: 1) it can only be performed using a contrast medium, 2) it is associated with significant radiation, and 3) it is less reliable in the presence of biliary obstruction or high serum bilirubin levels. The use of CT cholangiography to detect a biliary complication should still be considered experimental.

3.3 Direct cholangiography

Direct cholangiography, either percutaneously or through endoscopic retrograde cholangiography (ERC), has been the gold standard for the detection of biliary abnormalities for a long time. It has the inherent advantage of biliary access to facilitate therapeutic measures. Since the use of a biliary drain (e.g. T-tube) is no longer routine practice in most transplant centers, ERC is a frequently used method to detect and treat biliary complications. However, over the last years the less invasive MRC is increasingly used when compared to ERC. There is no data to suggest that ERC after liver transplantation is associated with more complications than the use of ERC in the general population. Considering the safety, diagnostic yield, and therapeutic potential of ERC, this should be considered the preferred invasive method. In the presence of altered biliary anatomy, such as a Roux-Y hepatico-jejunostomy, ERC is more difficult to perform. In these cases, percutaneous transhepatic cholangiography (PTC) or PTC
drainage is a good alternative method to obtain adequate imaging of the bile ducts. In several series successful ERC in the presence of a Roux-Y reconstruction has been reported using either a normal duodenoscope or double-balloon endoscopes.\textsuperscript{33,34} PTC is most easily obtained in the presence of dilated bile ducts. In experienced hands, however, this can be a safe procedure also with undilated bile ducts.\textsuperscript{35} It not only allows adequate imaging of the bile ducts, but also provides access for therapeutic interventions such as balloon dilatation (as discussed below).

**3.4 Hepatobiliary scintigraphy**

Hepatobiliary scintigraphy can be used as a diagnostic tool to detect post-transplant biliary obstruction and leakage. It has a sensitivity of approximately 60% for these indications.\textsuperscript{36} The main advantage is its non-invasive nature; its main disadvantage is low resolution and lack of direct visualization of the biliary anatomy. The sensitivity of hepatobiliary scintigraphy to detect NAS is not known. With the increasing use and availability of MRC, scintigraphy is today rarely anymore used to detect biliary strictures. It could still be of value in those patients in whom an obstruction at the level of the Roux-Y jejunal loop is suspected or when MRC is not possible (i.e. presence of a pacemaker).

**3.5 Other diagnostic tools**

Endoscopic ultrasonography is an emerging tool for the detection of hepatobiliary diseases. It has excellent diagnostic properties for the distal bile duct. Endoscopic intraductal ultrasonography can be used for the characterization of intraductal abnormalities. Use of these techniques in liver transplant recipients is still anecdotal. A potentially more valuable tool is direct cholangioscopy. With this technique, a small endoscope (cholangioscope) can be advanced through a normal duodenoscope to directly visualize the bile ducts. This can provide information about the biliary epithelium and the presence of stones, sludge and strictures. It can also be a therapeutic tool to advance guide wires or to remove bile duct stones. The number of indications for these highly specialized techniques, however, is still limited.
4. Pathogenesis, clinical presentation, and management

A broad variety of biliary complications can occur after liver transplantation and the pathophysiology is often multifactorial. Its presentation may be aspecific and physicians can identify biliary complications by one or more of the following symptoms: abdominal pain, cholangitis, elevated liver enzymes and jaundice if the bile duct becomes obstructed. In general, critical mechanisms in the development of post-transplant cholangiopathy include ischemia-reperfusion injury, altered and therefore toxic bile salt composition, insufficient protection by the HCO₃- umbrella, an insufficient regeneration of the biliary epithelium by cholangiocytes and peribiliary glands, and different immune-mediated injuries. Each of these mechanisms can concomitantly contribute to bile duct damage during and after liver transplantation and result in subclinical and clinical manifestations. Accordingly, various biliary complications overlap and share common pathogeneses. For example, hepatic artery thrombosis (HAT) results in tremendous ischemical damage, loss of cholangiocytes, and bile duct wall necrosis. NAS, casts, and eventually, intrahepatic bile duct leakage can develop. In this case, loss of the epithelial barrier leads to infiltration of toxic bile into the bile duct wall and this in turn causes more bile duct damage, necrosis, and intrahepatic biloma formation. Casts develop from the cumulating epithelial cells that are sloughed off from the bile duct wall. However, NAS are not always preceded by HAT and intraductal casts and sludge can be detected without signs of NAS. This explains the heterogeneity of biliary strictures and therefore we propose the term post-transplant cholangiopathy to describe the spectrum of pathologies of the larger bile ducts in the absence of hepatic artery thrombosis or stenosis without signs of recurrent diseases (i.e. primary sclerosing cholangitis). A complete classification of biliary complications after transplantation is depicted in Box 32.1, of these, the most common types are biliary leakage and bile duct strictures.

4.1 Biliary leakage

Pathogenesis and clinical presentation

Bile leakage after liver transplantation is reported in 1–25% of recipients. The incidence of bile leakage is the highest after transplantation of a split liver or a graft from a living donor due to the hepatic resection surface.²⁹,³⁷ Bile leakage can either be symptomatic or asymptomatic, and may be discovered coincidentally on a postoperative
cholangiogram. Symptomatic patients may present with abdominal pain, localized or generalized peritonitis, fever, and sometimes elevated serum liver enzymes and/or bilirubin. Biliary leakage can occur at various sites and intervals after transplantation. The majority of postoperative leaks occur at the site of anastomosis or the T-tube insertion site, but also the resection surface of the graft in case of a living-donor or a split-donor transplantation is a common site for leakage. Bile leakage early after liver transplantation most likely originates from the anastomosis or the T-tube insertion site. Anastomotic leaks are mainly related to errors in surgical technique and/or ischemic necrosis at the end of the bile duct. Insufficient blood supply or traction of the stitches causes ischemia, which can result in bile leakage. A hepatic artery thrombosis can lead to massive biliary necrosis resulting in dehiscence of the biliary anastomosis. Bile leakage at the T-tube insertion site can occur immediately after transplantation or after removal of the T-tube due to an insufficiently formed fistula around the tract of the bile drain. Occasionally, bile leakage occurs after percutaneous liver biopsy or iatrogenic duct damage.

**Management**

The management of bile leaks depends on the type of biliary anastomosis, clinical presentation, severity, and localization of the bile leak. The majority of bile leaks are due to leakage at the site of the biliary anastomosis. If a leak presents shortly after surgery, ultrasonography should be made to confirm arterial perfusion of the graft.

A small anastomotic bile leak can sometimes be managed conservatively, especially when the patient is asymptomatic. Early anastomotic leakage can best be treated by a relaparotomy and a surgical revision of the biliary anastomosis. Symptomatic or infected bile collections should be treated with a radiologically placed percutaneous drain. An anastomotic bile leak without disruption of the anastomosis can be successfully managed primarily nonsurgically. Stenting of the bile duct, nasobiliary drainage, sphincterotomy and a combination of these have all been used with a success rate of 85–100%. Since sphincterotomy may lead to specific complications (bleeding and perforation), it should not be routinely performed. The optimal timing of stent removal after resolution of symptoms is still unclear, but 8 weeks has been proven successful.38
In the presence of a hepatico-jejunostomy, ERCP can be attempted, but is frequently not successful. Alternatively, a PTC drain can be placed, even in the presence of non-dilated bile ducts. In the rare case of a complete disruption of the anastomosis, prompt surgery with conversion to a hepatico-jejunostomy is most appropriate. In selected cases a repeat choledochocholedochostomy can be considered. In the case of diffuse bilious peritonitis with hemodynamic instability or sepsis, direct laparotomy should always be considered. Leakage after removal of a bile drain can be managed successfully in one-third of cases by conservative measures, including intravenous fluids, antibiotics, analgesics, and observation. In the absence of improvement, ERCP with stent placement should be performed. A laparotomy is indicated when clinical signs of biliary peritonitis persist despite adequate drainage of the biliary system.

4.2 Anastomotic stenosis

Pathogenesis and clinical presentation

Isolated strictures at the site of the bile duct anastomosis, so-called anastomotic strictures, are reported in 4–9% of patients after liver transplantation. In general, anastomotic strictures do not remain subclinical and are detected after the occurrence of cholestatic laboratory liver function tests, jaundice, or cholangitis. Anastomotic strictures are thought to result mainly from surgical technique and/or local ischemia, leading to fibrotic scarring of the anastomosis. Surgical factors include inadequate mucosa-to-mucosa adaptation at the anastomosis and damage of microvascularization due to dissection too close to the bile duct. To minimize the risk of local ischemia at the distal end of the donor choledochal duct, the bile duct should therefore remain surrounded by an adequate amount of tissue. Generalized hepatic ischemia due to hepatic artery thrombosis can also result in anastomotic stricturing. Other risk factors for the development of anastomotic structures are anastomotic bile leakage after transplantation and a sex mismatch between donor and recipient. Liver transplantation using a split graft or a liver derived from a living donor is associated with a higher risk of developing an anastomotic bile duct stricture, because of the frequent discrepancy between the diameter of the hepatic duct of the graft and choledochal duct in the recipient. In addition, vascularization of the hepatic duct can be
compromised when a partial graft is derived from a living donor or split liver. These and other surgical aspects of living-donor and split-liver transplantation are discussed in more detail in chapters 23 and 24.

**Management**

The most frequently used therapeutic approach to an anastomotic stricture is endoscopic balloon dilatation and stenting of the stenosis. This treatment has been widely studied and is both safe and effective. Technical success is obtained in 90–100%, and long-term resolution of the stricture in 70–100% of cases.\(^4\) Although disputed by some, most centers obtain the best results with a protocol of progressive stenting every 8–12 weeks with increasing numbers and diameters of stents until resolution of the stenosis is obtained.\(^4\) In some cases, the stenosis recurs despite effective initial therapy. Some centers have used a covered expandable metal stent to treat a refractory biliary stenosis after transplantation. This, however, is not routine practice. Presentation of an anastomotic stricture more than 6 months after transplantation and previous bile leakage at the site of the anastomosis are risk factors for difficult-to-manage strictures.\(^4\) When an anastomotic stenosis does not respond to repeated dilatation and stenting, surgical revision or conversion to a Roux-en-Y hepatico-jejunostomy anastomosis is a good alternative with excellent long-term success.\(^4\) Incidentally, narrowing at the anastomosis can be detected while it remains unclear whether this is a clinically relevant stricture. In such cases, a short trial of stenting can be of value.\(^4\)

In the presence of a hepatico-jejunostomy, where the anastomosis is not easily accessible by endoscopy, percutaneous transhepatic treatment by balloon dilatation and temporary stenting is usually successful. This approach can also be used after split-liver or living-donor liver transplantation, although results are not as good, possibly because compromised microvascularization and local ischemia are more frequently the underlying cause.\(^4\)

**4.3 Post-transplant cholangiopathy**

The term post-transplant cholangiopathy covers multifocal biliary abnormalities after liver transplantation that include NAS, intraductal sludge and casts, and bile duct necrosis with intrahepatic leakage and biloma formation.\(^4\) These bile duct abnormalities
represent different aspects of the post-transplant cholangiopathy with necrosis of the bile duct wall and subsequent leakage of bile into the liver parenchyma being the most severe side of the spectrum. Other terms used in literature that attempt to describe post-transplant biliary abnormalities are ischemic-type biliary lesions (ITBL) and ischemic cholangiopathy. Yet the term post-transplant cholangiopathy is preferred since the pathogenesis is believed to be multifactorial and cannot always be identified.

4.3.1 Non-anastomotic strictures

Pathogenesis and clinical presentation

NAS are strictures at any location in the donor bile duct other than the anastomosis. Biliary strictures may be confined to the hepatic bifurcation, but may also present as a more diffuse type including narrowing of the more peripheral bile ducts in the liver. This type of bile duct strictures is regarded as the most troublesome biliary complication as the strictures are often resistant to therapy and one of the most frequent indications for retransplantation. As stated before, NAS can be accompanied by intraductal sludge or cast formation. The clinical presentation of patients with NAS is often not specific; symptoms may include fever due to cholangitis, abdominal complaints, and increased cholestatic liver function tests, either with or without clinical jaundice. The reported incidence of NAS after liver transplantation varies between different studies, ranging from 1–20%, which can partly be explained by variations in the definition of NAS used in different studies. About half of all NAS occur within 1 year after transplantation, and the remainder can be detected up to several years after transplantation. In livers obtained from DCD donors, the incidence of NAS is about 10% higher and they may occur earlier than in livers obtained from DBD donors.

Knowledge about the pathogenesis of NAS is slowly emerging from clinical and experimental studies. Several risk factors for this type of biliary complication have been identified, strongly suggesting a multifactorial origin. In general, the mechanisms underlying NAS can be grouped into three categories: 1) preservation or ischemia related damage to the bile duct wall without sufficient regeneration of the biliary epithelium 2) cytotoxic injury induced by hydrophobic bile salts, and 3) immune-mediated injury.
These pathological mechanisms contribute, whether simultaneously or not, to disastrous damage of the biliary epithelium. Generally, in case of epithelial loss, cholangiocytes proliferate in an attempt to repopulate the decayed epithelium. However, if the damage is detrimental to almost all cholangiocytes, this mechanism alone cannot restore the integrity of the bile duct. As a second repair mechanism, stem cells situated in the peribiliary glands are activated to proliferate and differentiate and thereby restore the epithelial lining. These stem cells are resistant to ischemia and reside in the bile duct wall grouped together in small islets, the peribiliary glands. In progression to post-transplant cholangiopathy, also this resource of new cholangiocytes falls short, which makes the uncovered and unprotected bile duct wall susceptible for intrusion of toxic bile salts and infections. Damage to the PVP due to ischemia and histological injury to the peribiliary glands have been associated with the development of NAS. The lack of adequate supply of oxygen and nutrients in this case could explain the poor regeneration by the peribiliary glands. However, further studies are required to understand why this second mechanism tends to fail in course of biliary strictures or other biliary complications.

In one large clinical study in which patients were grouped based on the time interval between transplantation and the occurrence of NAS, it was suggested that ischemia-mediated mechanisms are mainly responsible for the development of NAS within the first year after transplantation, whereas immune-mediated mechanisms play a more important role in the pathogenesis of strictures occurring beyond the first year.

The high incidence of post-transplant cholangiopathy after DCD liver transplantation and the radiologic similarities between the bile duct abnormalities of NAS and bile duct abnormalities seen in the presence of hepatic artery thrombosis strongly suggest an ischemic factor in the origin of these strictures. The relevance of adequate blood supply and the impact of ischemia on the bile ducts have been discussed in more detail in paragraph 2.1 (Organ procurement and preservation).

Another relevant factor in the pathogenesis of post-transplant cholangiopathy is toxicity caused by hydrophobic bile salts. Hydrophobic bile salts have potent detergent properties towards cellular membranes of hepatocytes and biliary epithelial cells. Under physiological circumstances the toxic effects of bile salts are prevented by complex formation with phospholipids and cholesterol (mixed micelle). However, early after liver transplantation, the balance in biliary excretion of these three components is disturbed,
leading to the formation of more toxic bile. Evidence for a pivotal role of bile salt-mediated toxicity in the pathogenesis of bile duct injury and subsequent bile duct stricturing has gradually emerged during the last decade. Both experimental animal studies and clinical studies have demonstrated that biliary bile salt toxicity early after transplantation is associated with the development of microscopic as well macroscopic bile duct injury. Bile salt toxicity acts synergistically with ischemia-mediated injury of the biliary epithelium without sufficient regeneration.

In this view, nontoxic hydrophilic bile salts (e.g. ursodeoxycholic acid) may have positive effects on the incidence of post-transplant cholangiopathy. In a randomized clinical trial, administration of ursodeoxycholic acid early after DCD transplantation did not decrease the incidence of NAS. Interestingly, however, biliary sludge and casts where significantly diminished within the first year postoperative. More (large) studies are needed to confirm a positive effect of administration of nontoxic bile salts to liver transplant recipients on post-transplant cholangiopathy. Several studies have provided evidence for an immunologic component in the pathogenesis of NAS. NAS have been associated with various immunologically mediated processes, such as ABO-incompatible liver transplantation, pre-existing diseases with a presumed autoimmune component (such as primary sclerosing cholangitis and autoimmune hepatitis), cytomegalovirus infection, chronic rejection, and finally with a genetic polymorphism in one of the CC chemokine receptors.

Management

In contrast to anastomotic strictures, NAS are much more heterogeneous in localization and severity. General recommendations regarding management are hard to make, and good-quality prospective studies are rare. In the case of diffuse and severe biliary strictures with progressive jaundice and bacterial cholangitis or biliary fibrosis, usually re-transplantation is the most favorable option. In most patients, the strictures are more localized and cirrhosis has not yet developed. Many cases are amenable to endoscopic therapy. In endoscopic therapy, repeated endoscopies with balloon dilatation and multiple stents are used. With this approach, success rates are 50–75%. As in anastomotic strictures, PTC can be used when endoscopic access is not feasible. In case of NAS that are confined to the extrahepatic bile ducts, surgical resection of the diseased
part and construction of a hepatico-jejunostomy should be considered. In case of recurrent cholangitis, maintenance antibiotics may result in long-term relief of symptoms. Although widely used, there is no clinical evidence that supports the use of ursodeoxycholic acid. While most types of biliary complications can usually be managed successfully (either surgically or by endoscopic techniques) or run a self-limiting course, NAS remain the most challenging type of biliary complication, as they are frequently therapy resistant and frequently associated with long-term sequelae. Up to 50% of patients with NAS either die or require retransplantation. Mortality rates differ markedly among studies.23

4.3.2 Biliary casts and sludge

Biliary casts and sludge are frequently found in company of NAS and can be considered as a sequel of bile duct strictures although they could also appear independently or in combination with other pathologies. Casts and sludge present as filling defects on cholangiography. Sludge is a viscous collection of mucus, calcium bilirubinate, and cholesterol. When left untreated, biliary casts can develop. Casts consist of retained lithogenic material morphologically confined to bile duct dimensions. Biliary sludge and casts tend to occur within the first year after transplantation.

Multiple factors may contribute to sludge and/or cast formation, including ischemia, infection, and preservation injury.5 Theoretically, anything that increases the viscosity of bile or reduces bile flow can predispose to casts or sludge. It is likely that ischemia contributes to the formation of casts or sludge both through stasis of bile (as a result of strictures) and through its direct injury to the biliary epithelium, resulting in the release of cell debris into the bile duct lumen as well as increasing the epithelial susceptibility to precipitation of lithogenic materials. Other pathogenic factors that are associated with casts or sludge are biliary cholesterol content, bacterial infection in relation to stents, the presence of a hepatico-jejunostomy, fungal infections and the use of cyclosporine.23 Regardless of the cause of casts or sludge after transplantation, an incidence of 5.7% was reported in the largest study so far, including 1650 transplanted livers.52 Most patients with biliary casts and/or sludge present with cholangitis and only a small percentage present with abdominal pain. Despite the relative infrequency, studies have shown an increased rate of morbidity and mortality as a result of biliary sludge and
casts, which have caused recurrent cholangitis, repeated need for surgery, graft loss, and death.\textsuperscript{53}

Intraductal casts and sludge of the biliary tree can almost universally be managed successfully by endoscopic removal. However, the long-term success of this treatment will depend on the underlying cause. If the formation of casts or sludge is caused by a local obstruction such as a biliary drain or an anastomotic stricture that can be treated successfully, removal of the obstruction may be curative. However, when biliary casts or sludge are a symptom of ischemic bile duct injury, the severity of the latter will determine the long-term success of cast removal and will determine the fate of the graft.

4.4 Biliary abnormalities due to hepatic artery stenosis or thrombosis

HAT is the most common and serious vascular complication with a reported incidence that varies between 2\% to 11\%.\textsuperscript{54,55} More detailed information regarding vascular complications can be found in chapter 31, however, we will cover shortly the main impact on the post-transplant bile duct in this chapter. To obtain a sufficient amount of oxygen and nutrients, the biliary tree relies on blood supply from the hepatic artery and the arterial branches of the gastroduodenal artery. These arteries continue in a fine vascular network encircling the bile duct, called the peribiliary vascular plexus. After transplantation, blood supply to the bile ducts depends entirely on the hepatic artery. Accordingly, in case of HAT, the bile duct experiences widespread ischemia, which may result in necrosis and eventually bile leakage. HAT can be divided in 2 categories: early HAT and late HAT, with the timeframe used in literature varying between 2 weeks and 100 days after transplantation.\textsuperscript{56,57} Whereas late HAT may have a relative mild course due to the formation of vascular collaterals, early HAT is associated with widespread biliary ischemia and subsequent necrosis and bile leakage. Nevertheless, biliary complications may result late after the diagnosis of HAT and successful restorations of arterial flow to the liver.

4.5 Biliary strictures due to recurrent disease

Recurrent primary sclerosing cholangitis (PSC) may be another cause of biliary strictures occurring late (>6–12 months) after transplantation. A large retrospective multicenter analysis evaluating the incidence of biliary strictures after OLT in a cohort of PSC patients reported an incidence of 36.1\%.\textsuperscript{58} This is approximately 3.5-fold higher
than in non-PSC patients. More detailed information regarding recurrent diseases of the bile duct can be found in chapter 36.

4.6 Bacterial cholangitis

Bacterial cholangitis is not uncommon in immunosuppressed liver transplant patients and can result in a life-threatening illness. In general, the risk of cholangitis is increased in patients in whom a T-tube is used, in patients who underwent a hepatico-jejunostomy, and in patients complicated by anastomotic or NAS. All of these conditions may facilitate ascending migration of bacteria into the biliary tree. When a biliary drain is present, positive bacterial cultures from the bile may support the diagnosis, although it should be noted that colonization of bile is not infrequent. In other patients the diagnosis cholangitis is rarely supported by positive bile cultures and usually made after exclusion of other causes of fever. Bacterial cholangitis after liver transplantation usually presents with high fever with or without chills in combination with cholestatic liver function test. Management of acute cholangitis after transplantation is similar to that recommended to nontransplant patients and should include appropriate antibiotic therapy after the exclusion of an anatomical cause (e.g. anastomotic strictures).

5. Summary

Biliary complications are a frequent cause of morbidity after liver transplantation. Advances in surgical techniques and preservation methods during the last decades have led to better results, but biliary complications still occur in 10–40% of the recipients and are associated with mortality rates of 8–15%. Partial liver grafts (e.g. split livers and livers from living donors) as well as livers from extended-criteria donors (e.g. DCD donors) are associated with a relatively high risk of biliary complications. Of all biliary complications, bile duct strictures and bile leakage are most common after liver transplantation. While bile leakage and anastomotic bile duct strictures can usually be managed successfully without long-term sequelae, NAS are the most troublesome type of biliary complications. NAS are often multifocal and can be difficult to treat by endoscopic techniques. When associated with recurrent cholangitis, jaundice or even secondary biliary fibrosis, retransplantation may be the only treatment option left.
Future studies should focus on better defining the mechanism underlying NAS and on the development of effective preventive measures. In this respect, development and potential implementation in liver transplant protocols of machine preservation is of great relevance.
References


